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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,534	01/05/2005	Heikki Joensuu	ON/4-32326A	7483

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,534	JOENSUU, HEIKKI	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21 September 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 25-29 are presented for examination.

Acknowledgement is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP03/00802, filed January 27, 2003, which claims priority under 35 U.S.C. 119(a-d) to United Kingdom Patent Application No. 0201882.8, filed January 28, 2002, of which a certified copy was filed January 26, 2004.

Applicant's Information Disclosure Statement (IDS) filed September 21, 2006 has been received and entered into the present application. As reflected by the attached, completed copy of form PTO-1449 (three pages total), the Examiner has considered the cited references.

Applicant's response filed December 4, 2008 to the requirement for restriction/election dated June 7, 2007 has been received and entered into the present application. Upon reconsideration, the requirement for restriction/election dated June 7, 2007 was withdrawn in lieu of the new requirement for restriction/election dated February 15, 2008. Applicant's response filed March 12, 2008 to the requirement for restriction/election dated February 15, 2008 has been received and entered into the present application.

Applicant traverses the requirement for restriction, stating that the response filed December 4, 2007 limited the pending set of claims solely to instant claims 25-29, directed to a method for treating humans suffering from rheumatoid arthritis, and, therefore, the new restriction requirement dated February 15, 2008 appears to be an error.

In view of the fact that that amended claim listing of December 4, 2007 limited the scope of the claimed subject matter to a single invention, the requirement for restriction/election dated February 15, 2008 is rendered **MOOT**. Accordingly, claims 25-29 are presently under examination.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 25 is directed to a method of treating humans suffering from rheumatoid arthritis which comprises administering to said human in need of such a treatment a dose of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof.

In particular, there is insufficient antecedent basis for the limitation "the formula I" as recited in line 4 of claim 25, since the preceding text of the claim fails to reference "a formula I" *per se*.

Further, it is additionally unclear as to what "the formula I" refers, since claim 25 in which this limitation appears fails to present any structural depiction of formula I such that one of ordinary skill in the art at the time of the invention would have been reasonably apprised of the subject matter for which Applicant is presently seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, the limitation "the compound of formula I" will be interpreted to refer to the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 26 is directed to the method of claim 25, which is a method of treating humans

suffering from rheumatoid arthritis comprising administering to said human in need of such a treatment a dose of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof, wherein the compound of formula I is in the form of the monomethanesulfonate salt.

In particular, there is insufficient antecedent basis for the limitation "the monomethanesulfonate salt" as recited in line 2 of claim 26, since independent claim 25 from which claim 26 depends fails to set forth any reference to a "monomethanesulfonate salt" *per se*.

For this reason, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is, thus, properly rejected.

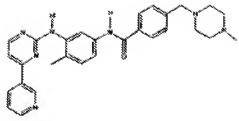
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 25 is rejected under 35 U.S.C. 102(e) as being anticipated by Moussy et al. (WO 03/002109 A2; Published January 2003, Priority to U.S. Provisional Patent Application No. 60/341,273, filed December 20, 2001, already of record).

Moussy et al. teaches a method for treating autoimmune diseases, such as, *inter alia*, rheumatoid arthritis (p.9, l.15-27 and p.10, l.18-20; instant claim 25), comprising the administration of an effective amount of the compound CGP57148B, also known as 4-(4-methylpiperazine-1-ylmethyl)-N-[4-methyl-3-(4-pyridine-3-yl)pyrimidine-2-ylamino)phenyl]-benzamide (p.8, l.14-18; instant claim 25), which has the

following chemical formula:  (p.8, l.18-20), to mammals in need of such treatment (abstract), preferably humans (p.12, l.16-17; instant claim 25).

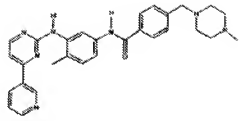
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moussy et al. (WO 03/002109 A2; Published January 2003, Priority to U.S. Provisional Patent Application No. 60/341,273, filed December 20, 2001, already of record) in view of Remington's Pharmaceutical Sciences (Sixteenth Edition, 1980; p.420-425) and Zimmerman et al. (WO 99/03854; 1999).

Moussy et al. teaches a method for treating autoimmune diseases, such as, *inter alia*, rheumatoid arthritis (p.9, l.15-27 and p.10, l.18-20; instant claim 25), comprising the administration of an effective amount of the compound CGP57148B, also known as 4-(4-methylpiperazine-1-ylmethyl)-N-[4-methyl-3-(4-pyridine-3-yl)pyrimidine-2-ylamino)phenyl]-benzamide (p.8, l.14-18; instant claim 25), which has the

following chemical formula:  (p.8, l.18-20), to mammals in need of such treatment (abstract), preferably humans (p.12, l.16-17; instant claim 25).

Moussy et al. fails to teach the use of the monomethanesulfonate salt of the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide (claim 26) or the specific dosage amounts and/or frequency of administration instantly claimed (claims 27-29).

Remington's Pharmaceutical Sciences (p.420-425) teaches that drugs are formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (col.2, p.424, para.1).

Zimmerman et al. teaches an essentially pure crystal form (i.e., the beta-crystal form) of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2ylamino)phenyl]-benzamide (p.3, para.3-p.4, para.1), which is necessarily a *mono*methanesulfonate salt as instantly claimed as evidenced by the chemical structure presented at p.4, which contains a single methanesulfonate molecule. Zimmerman et al. further teaches that, depending on the species, age, individual condition, mode of administration, and the clinical picture in question, effective doses of the disclosed compound, e.g., daily doses of about 1-2500 mg, preferably 1-1000 mg, especially 5-500 mg, are used in warm-blooded animals of about 70 kg bodyweight (p.17, para.1).

One of ordinary skill in the art at the time of the present invention would have found it *prima facie* obvious to employ a salt formulation of the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide, such as the monomethanesulfonate

salt disclosed by Zimmerman et al. because, as evidenced by Remington's, pharmaceutical salt formulations are known to modify the duration of action of a drug, modify the transportation and distribution of the drug in the body, reduce toxicity, and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself. Thus, it would have been *prima facie* obvious to the skilled artisan motivated by any one or more of these factors to formulate the disclosed 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide compound of Moussy et al. into a pharmaceutically acceptable salt, such as the monomethanesulfonate salt of Zimmerman et al., to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the parent compound itself.

Furthermore, one of ordinary skill in the art at the time of the present invention would have found it *prima facie* obvious to use the methanesulfonic acid addition salt of in a daily dosage amount of, for example, 1-2500 mg, because such a daily dosage amount was known to be pharmacologically active as evidenced by Zimmerman et al. Though such an amount is not explicitly identical to those amounts instantly claimed (see, e.g., claim 27, directed to the monomethanesulfonate salt at a daily dose of 100-1000 mg of the free base, or claim 28, directed to the monomethanesulfonate salt at a daily dose of 200-800 mg of the free base), the determination of the optimal amounts of the active agent would have been a matter well within the purview of, and *prima facie* obvious to, one of ordinary skill in the art at the time of the invention. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the amount that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the

currently claimed specific amounts are not seen to be inconsistent with that which would have been determined by, and well within the routine skill of, the skilled artisan.

Additionally, the concentration of the active ingredients is a result-effective variable, i.e., a variable that achieves a recognized result, and, therefore, the determination of the optimum or workable dosage range would be well within the practice of routine experimentation by the skilled artisan, absent factual evidence to the contrary, and, further, absent any evidence demonstrating a patentable difference between the compositions used and the criticality of the amount(s). In further support thereof, Applicant's attention is directed to the MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges in the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Although the present claims are directed to milligram concentrations, such a motivation is nonetheless relevant.

Moreover, the artisan would have been further motivated to administer the disclosed compound of Moussy et al. daily for a period exceeding three months because rheumatoid arthritis is a chronic disease that requires persistent and long-lasting treatment to control and modify the symptoms of the disease such that the symptoms are more or less tolerable to the afflicted patient.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the publication to Eklund et al. ("Treatment of Rheumatoid Arthritis with Imatinib Mesylate: Clinical Improvement in Three Refractory Cases", *Annals of Medicine*, 2003, 35(5):362-367).

Rejection of claims 25-29 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

May 27, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614